UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/509,779	03/29/2000	YI SUN	5650-01-MJA	9770

7590 11/12/2003

MICHAEL J ATKINS
WARNER LAMBERT COMPANY
2800 PLYMOUTH ROAD
ANN ARBOR, MI 48105

EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 11/12/2003

21

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/509,779	Applicant(s) Sun
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 22, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *2-6, 8-17, 25, 26, 32, and 38-42* is/are pending in the application.

4a) Of the above, claim(s) *41* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *2-6, 8-17, 25, 26, 32, 38-40, and 42* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *18*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Amendment filed September 22, 2003 (Paper No. 20) in response to the Office Action of March 19, 2003 (Paper No.17) is acknowledged and has been entered. Previously pending claims 1, 7, 18-24, 27-31, 33-37 have been canceled, claims 2, 8, 25, 26, 39, 40 have been amended and new claims 41-42 have been added. Claim 41 has been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention. Claims 2-6, 8-17, 25-26, 32 and 38-40, 42 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Since applicant has already elected a group for action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, the embodiments of claim 41 drawn to a method for inhibiting tumor growth have been withdrawn from consideration as being directed to a non-elected invention and only the previously elected and examined group will be examined. See 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03. Newly submitted claim 41 is directed to an invention that is independent or distinct from the invention originally claimed because it is drawn to a materially distinct method which differs at least in objectives, method steps, reagents and/or dosages and/or schedules used, response variables, and criteria for success from the methods previously elected. Further, the newly added invention and the claimed polynucleotides are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (I) the process for using the product as claimed can be practiced with

another materially different product or (ii) the product as claimed can be used in a materially different process of using that product [see *MPEP* § **806.05(h)**]. In the instant case the polynucleotide products as claimed can be used in a materially different process such as expression of polypeptides encoded by the claimed polynucleotides.

3. The following objection is maintained.

Objection to reference to the drawings in the instant specification is maintained for the reasons of record. Applicant argues that a facsimile, attached as Exhibit A states that all drawings were submitted upon the request of the Examiner having previously been submitted at the filing date, accordingly the requirement to delete all figures is obviated and withdrawal is requested. The argument has been considered but has not been found persuasive because a review of the submitted Exhibit A reveals only that the drawings that Examiner had requested were being submitted. No evidence has been submitted demonstrating that the drawings were submitted with either the instant specification as originally filed, or the parent application, as originally filed, to which priority is claimed. Applicant is required to delete all mention of figures since it appears that they were never submitted and if now submitted would be new matter.

4. The following rejections are maintained:

Claim Rejections - 35 USC § 112

5. Claims 6 and 12-14 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 17, Section 5, pages 2-3.

Applicant argues that the statement on page 8 of the Response obviates the rejection. The argument has been considered but has not been found persuasive because Applicant does not state which deposited host cells are covered by the statement. Further, Applicant has not met the formal requirements delineated in Paper No. 13, Section 10, pages 5-6 wherein Applicant is required to refer to the deposit in the body of the specification and to identify the deposit by accession number, the name and address of the depository as well as the complete taxonic description.

6. Claims 2, 4-5, 8, 10-11, 25-26, 32, 39-40 remain rejected under 35 USC 112, first paragraph and newly added claim 42 is rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 17, Section 6, pages 3-5.

Applicant argues that the specification discloses both heme binding sites and zinc finger domains and states that the zinc finger domain protects cells against apoptosis. The argument has been considered but has not been found persuasive because the claim is not drawn to a correlation of any structure and function as required. When Applicant argues that the zinc finger domain protects cells against apoptosis and that the heme binding site in the SAG protein acts as an oxygen radical scavenger to prevent oxygen radical induced damage, Applicant is arguing limitations not recited in the claims as currently constituted. Further, given the teachings of Swaroop et al (Free Radical Biology and Medicine, 1999, 27:193-202) wherein it is stated that "it appears that SAG protein does not bind heme", it is unclear how the putative heme binding site could be involved with oxygen scavenging.

Applicant further argues that although the GCG program as disclosed in Example 2 does not identify any functional domains in the putative encoded polypeptide, this finding should not be construed to limit the scope of the claims because, as taught the specification, in the apoptosis protective function and the lipid peroxidation protective function are linked to the structures of the zinc finger domain and heme binding sites respectively on SAG. The argument has been considered but has not been found persuasive. The GCG program findings disclosed in the specification raise serious doubt as to the functions of the polypeptide encoded by the claimed polynucleotides for the reasons of record, especially in view of the teachngs of Swaroop et al, *Supra*. Further, Applicant is once again arguing limitations in the claims not recited in the claims as currently constituted.

The arguments have been considered but have not been found persuasive and the rejection is maintained

7. Claims 2, 4-5, 20-22, 32, 38-40 remain rejected under 35 USC 112, first paragraph and newly added claim 42 is rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 17, Section 8, pages 5-16.

Applicant directs Examiner's attention to the fact that the claims are not directed to the treatment of cancer *per se* but that the present application fully enables newly added claim 41 which is supported in the specification. Examiner appreciates Applicant's point but notes that claim 41 has been withdrawn from consideration as not being previously presented. Examiner discussed therapeutic applications only in an attempt to establish whether or not the claimed

polynucleotide or polypeptides encoded thereby were useful. For the reasons of record, they are not.

Applicant argues that most of the references cited were published in 1994-1995 and directs Examiner's attention to the fact that the present invention was filed in March of 2000 and that the relevant technology had significantly advanced from 1995 to 2000 and that the alleged unpredictability illustrated by the references is at best general and cannot negate the specific successful invention embodied in the present claims. The argument has been considered but has not been found persuasive because Applicant presents no objective evidence that demonstrates that the findings in those references were not relevant to the invention at the time the invention was made and for the reasons of record, Applicant has not disclosed a specific successful invention.

Applicant argues that the specification provides sufficient teaching using to enable those skilled in the art to make and use the claimed invention. The argument has been considered but has not been found persuasive for the reasons of record.

Applicant argues that there is no requirement for the present application to include human or clinical trial data. The argument has been considered but not found persuasive because although neither human nor clinical trial data is required, since the data presented is cell culture data and is not correlative with the *in vivo* condition the rejection is maintained for the reasons of record. Further, the argument is moot given that claim 41 has been withdrawn from consideration.

Applicant has amended the paragraph in Example 19, starting on page 232, line 24 to insert the term "can" for the term "may" and as such Applicant submits

that the present invention teaches that SAG proteins will function as claimed. The argument has been considered but has not been found persuasive since amendment of the specification to recite new matter does not enable anything.

The arguments have been considered but have not been found persuasive and the rejection is maintained.

8. Claims 15-17, 25-26, 32, 38 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 17, Section 9, pages 16-18.

Applicant argues that (a) the present invention also provides DNA molecules substantially similar to those shown in SEQ ID NO:1 or SEQ ID NO:3, (b) the mutants can be used to direct expression of the SAG protein and for mutational analysis of SAG protein function, (c) the specification teaches that the SAG deletion mutants not only associate with cancer, but also are tumor-specific mutations. Further, the specification teaches methods of introducing into tumor cells expression vectors comprising a DNA that is antisense to a sequence substantially similar to the DNA molecule set forth in SEQ ID NO:1 or SEQ ID NO:3, (d) Applicant submits that the specification provides an adequate teaching regarding the generation of SAG mutants as well as therapeutic uses for antisense SAG mutants, (e) that SAG mutations are cancer specific and can be used for diagnosing cancer, (f) Applicant reiterates cell culture studies drawn to the SAG, (g) although no working examples are provided, 35 USC 112, first paragraph does not require an applicant to provide all the detailed procedures for making and using the invention.

The arguments have been considered but have not been found persuasive because (a') although the specification provides DNA molecules that are substantially similar to those in SEQ ID NO:1 or SEQ ID NO:3 the specification does not teach how to use those "substantially similar" molecules for the reasons of record, (b') (d') the use of the claimed mutants as research tools for mutational analysis of SAG protein function is not considered a real world use for the purposes of patentability, see MPEP 2107.01 and no real world use has been disclosed for proteins encoded by the claimed synthetic human SAG poynucleotides and the use of antisense therapy is not enabled for the reasons of record, (c') the teaching is not enabling for the reasons of record, (e') no SAG mutants associated with any primary cancer have been identified. Although SEQ ID Nos 11 and 13 were detected in cancer cell lines, for the reasons of record it cannot be predicted that those mutants would be found in primary cancer cells. Further, although the specification suggests that there are deletion mutants in primary colon carcinoma samples as compared with normal tissue controls, there is no teaching in the specification that the mutations were either the 7bp or 48 bp deletions found in either SEQ ID Nos 11 or 13 (f') cell culture data is not convincing for the reasons of record, (g') it is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the

invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling." Given the novelty of the claims invention and the lack of guidance in the specification, and in view of the complex nature of the claimed invention one of skill in the art would be forced into undue experimentation to practice the claimed invention.

New Grounds of Objection

9. The amendment filed September 22, 2003 is objected to under 35 U.S.C. § 132 because it introduces new matter into the specification. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is the amendment of the specification on page 32 wherein the term "may" was deleted and the term "can" was substituted. The amendment alters the scope of the specification and is not supported by the specification as originally filed. Applicant is required to cancel the new matter in the response to this Office action.

New Ground of Rejection

Claim Rejections - 35 USC § 101

10. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

11. Claims 2-6, 8-17, 25-26, 32 and 38-40 and 42 are rejected under 35 USC 101 because the claimed invention is not supported by a specific asserted utility, a substantial utility.

The disclosed utilities for the novel and isolated and purified "SAG" (Sensitive to Apoptosis Genes) encoding SAG proteins, that is SEQ ID NO:1 and hybridization variants attached to SEQ ID NO:1, SEQ ID NO:3 and hybridization variants attached to SEQ ID NO:3, the nucleotide sequences isolated from the human DLD-1 colon carcinoma cell line SEQ ID NOS 11 and 13, the synthetic deletion mutants produced to characterize the human SAG, SEQ ID NO:3, nucleic acids encoding the polypeptides encoded by the synthetic deletion mutants produced to characterize the human SAG of SEQ ID NO:3 include (a) the inhibition of tumor cell growth by administration of antisense SAG which assertion appears to be based on *in vitro* assay of antisense inhibition of tumor cell growth in cancer cells transfected with SAG (p. 31), (2) diagnosis of cancer by detecting deletion mutants of SAG polynucleotides which assertion appears to be based on the detected deletions mutants of SEQ ID NO:3 in the DLD-1 human colon carcinoma cell lines as well as the apparently prophetic example wherein it is suggested that mutations detected in colon tumor tissues but not in normal adjacent tissues indicate that they are tumor specific mutations and can be used as a diagnostic tool in the clinic (para bridging pages 33-34) as well as detection of similar deletion mutations in a testicular carcinoma cell line, (3) use of the encoded polypeptides as oxygen scavengers and zing ring finger binders which assertion appears to be based on the putative heme binding and zinc finger binding motifs identified in the encoded

protein SEQ ID NO:2, (4) protection of cells from apoptosis which assertion appears to be based on *in vitro* studies of the sensitivity of human SAG-transfected cells to OP-induced apoptosis (p. 29). As previously noted, no data is presented for the observation that overexpression of SAG protein protects cells against OP induced apoptosis. The specification states that less DNA fragmentation was observed in wild-type SAG transfected cells compared to control cells. However, there is no way to evaluate the statements in the specification because it is unknown what constitutes "less" and whether or not that "less" is statistically significant or whether in fact SAG functions as suggested when expressed in cells *in vivo*. (5) The disclosed utilities of the encoded proteins include production of antibodies to that protein (p. 24). However, neither the specification nor any art of record teaches what the claimed polynucleotides or hybridization variants or encoded polypeptides are, what that they do, do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases. The asserted utility such as the production of antibodies applies to many unrelated encoded polypeptide structures. Therefore the asserted utility is not considered a "specific" utility, i.e. it is not specific to the encoded polypeptides. For the same reason, the utilities drawn to the heme binding motifs and the zinc finger binding motifs are not considered "specific" utilities because they are not specific to the encoded polypeptides. Examiner takes note that heme binding sites are found in a wide variety of proteins, including cytochromes, hemoglobin, nitrate reductase and heme oxygenase, with different structures and functions. In addition Examiner takes note of the ubiquitous expression of proteins with zinc finger binding domains that

function as transcription factors or RNA binders with different structures and functions. It is further noted that Swaroop et al, *Supra*, in an article published seven months after the earliest priority date of the instant application, specifically teach that although the SAG protein contains two putative heme-binding sites and a ring finger domain, the protein appears not to bind with heme and to lack transcription factor activity (see abstract), thus it appears that not only does the heme binding and ring finger domains not provide specific utility for the claimed invention, it also apepars that the putative heme binding domain doesn't even bind heme. It is again noted that, as drawn to the encoded polypeptide, motif searching of the deduced protein sequences using the GCG program did not reveal any known functional domains (p. 15, lines 27-30). It is clear from the teaching of the specification that the function of the encoded polypeptide is unknown. Thus, the invention drawn to methods of isolating the encoded polypeptides does not have substantial utility, because the utility of the encoded polypeptides is unknown. As drawn to the synthetic mutants of Claim 15, and the claims dependent upon claim 15, and the polynucleotides encoding the polypeptides encoded by the synthetic mutants, MPEP 2107.01 clearly states that a "substantial utility" defines a "real world" use,

> "Utilities that constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities..... Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved" ..... "have no specific and/or substantial utility."

Given the above, the deletion mutants claimed in claim 15, and the claims dependent upon claim 15, and the polynucleotides that encode polypeptides encoded by the deletion mutants in claim 15 do not have a substantial utility. The only utility identified for the mutants and the polypeptides encoded thereby, is for mutational analysis of human SAG function. No utility has been established for the claimed polynucleotides encoding the polypeptides encoded by these mutants. There is no teaching that these synthetic mutants are produced *in vivo*, there is no teaching that these synthetic mutants are any way associated with the etiology or progression of any disease. There is no teaching that any of these synthetic mutants produce a protein *in vivo* or what the function of that protein might be. As drawn to diagnosis of cancer with PCR of the polynucleotides of SEQ ID NO:1, hybridization variants attached to SEQ ID NO:1, SEQ ID NO:3, hybridizationvariants attached to SEQ ID NO:3, synthetic mutants disclosed in claim 15, cell culture variants, none of these polynucleotides have substantial utility as drawn to the diagnosis of cancer. In particular, the specification teaches the identification of two deletion mutants of SEQ ID NO:3 in a colon cancer cell line. For the reasons of record, there is no nexus between cell line mutational data and the *in vivo* condition, therefore, additional work must be done in order to establish that there is a nexus between colon cancer and deletion mutation of SEQ ID NO:3. Although the specification teaches in Example 21 that twelve pairs of colon carcinomas and adjacent normal tissues were collected from 12 patients, no data is presented. The example is worded in such a nebulous fashion that it is not possible to determine whether the statement that "Mutations detected in tumor tissues but not in normal adjacent

tissues indicate that they are tumor specific mutations and can be used as a diagnostic tool in the clinic for colon.....carcinoma." is drawn to an actual objective finding of utility or whether or not the example is simple a prophetic example and no utility has been established. As drawn specifically to SEQ ID NO:3, this rejection can be obviated by the submission of objective evidence demonstrating that SEQ ID NO:3 is found to be a deletion mutation in primary colon cancer cells compared to normal tissue. In addition, because of the disclosed lack of nexus between cell line mutational data and the *in vivo* condition, addition work must be done to determine whether the deletion mutations represented by SEQ ID Nos 11 and 13 are found *in vivo* in primary cancer cells, thus neither SEQ ID NO:11 or 13 has substantial utility and methods of using SEQ ID Nos. 11 and 13 do not have substantial utility. Further, the specification does not teach that these mutants are produced *in vivo*, there is no teaching that these mutants are any way associated with the etiology or progression of any disease. There is no teaching that any that these mutants produce a protein *in vivo* or what the function of that protein might be or that any polynucleotides produce a protein encoded by these mutants, thus polynucleotides that encode the polypeptides encoded by the mutants do not have substantial utility since additional work must be done to establish the function or even expression of these polynucleotides. It is noted that no nexus between SEQ ID NO:1, hybridization variants of SEQ ID NO:1 or any of the synthetic mutation constructs, and any form of cancer has been identified.

As drawn to protection against apoptosis, the sensitivity of human SAG-transfected cells to OP-induced apoptosis was assayed, the *in vitro* results suggest

that overexpression of SAG protein protects cells against OP9 induced apoptosis as less DNA fragmentation was observed in wild-type SAG transfected cells compared to control cells (p. 29). It is noted that no data is presented, thus there is no way to determine from the specification whether this identified difference is significant or how much "less" is observed. It is noted that this *in vitro* data was collected only using the polypeptide encoded by SEQ ID NO:3, there is no information drawn to any of the polypeptides encoded by the other claimed polynucleotides. Clearly, additional work must be done to establish whether or which encoded SAG protein gives protection against apoptosis, thus the invention lacks substantial utility.

As drawn to the use of the encoded protein as an oxygen radical scavenger, Example 19 states that the SAG protein demonstrates contains 12 cystein residues and forms disulfide bonds after exposure to hydrogen peroxide and SAG protein binds heme which can modulate oxidants by oxidation reduciton. This oxidative buffering activity **may** qualify SAG as an oxygen radical scavenger (emphasis added). It is noted that no oxidative buffering activity has been demonstrated and that as noted above, Swaroop et al, *Supra*, state that it appears that SAG protein does not bind heme. The specifciation then suggests an assay, in yeast, to determine whether SAG is an effective oxygen radical scavenger. Example 20 presents a protocol to determine whether SAG, in its putative scavenger capacity, can prevent IL-1beta induced brain injury during ischemia. Clearly, additional work must be done to establish whether encoded SAG protein is an oxygen radical scavenger, thus the invention lacks substantial utility. Further, even if it were to be established that the SAG protein is an oxygen scavenger, the encoded protein would not have

specific utility because of the whole universe of oxygen scavenging polypeptides known in the art.

Finally, neither the specification nor any art of record teaches what the polynucleotides or polypeptide encoded by said polynucleotides are, what they do in the real world, do not teach a relationship to any specific disease or establish any involvement of the claimed species in the etiology of any specific disease or teach which polynucleotides associated with SEQ ID NOS 1 and 3 would function as claimed in a diagnostic assay. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed nucleic acids and methods. Because the claimed invention is not supported by a specific asserted utility, a substantial utility, for the reasons set forth, credibility of any utility cannot be assessed.

11. Claims 2-5, 8-11, 25-26, 32, 39-40, 42 are rejected under 35 USC 101 because the claims are inoperable. The claims are drawn to SAG-associated species with heme binding sites. Inherent in heme binding site proteins is the binding of heme. However, Swaroop et al, *Supra*, specifically teaches that although SAG protein contains two putative heme binding sites, the protein appears not to bind with heme (see abstract). Given the above, since the protein containing the putative heme binding site appears to not bind heme, the claimed invention is inoperative.

12. Claims 2-5, 8-11, 25-26, 32, 39-40, 42 are rejected under 35 USC 101 because the claims are inoperable. The claims are drawn to isoalted and purified DNA molecules that hybridize to SEQ ID NO:1 or SEQID NO:3 under high stringency hybridization conditions wherein a polypeptide of protein encoded by

said DNA molecules comprises at least one heme binding site or one zinc finger domain. It is noted that any DNA molecule that hybridizes under the claimed stringent condition would be the complete complement of the portion of SEQ ID NO:1 or 3 to which it hybrizes. Although the specification discloses that SEQ ID NO: 1 and 3 encode polypeptides that comprise putative heme binding sites and zinc ring finger domains, the complete complement of those coding regions would not encode said polypeptides since the nucleotide sequences would not be the same. Given the above, the claimed inventions are inoperative. In the interests of compact prosecution, In the interests of compact prosecution, it is noted for Applicant's convenience that should the claims be amended to recite, for example, "DNA molecules whose complete complement encodes polypeptide with heme and/or zinc finger domain, that Hillier et al (W38711), Genbank Sequence Database (Acession W38711), National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland, publicly available May 15, 1996 teaches a DNA molecule which comprises 100% identity to SEQ ID NO:3, nucleoties 141-164 (which was found in us-09-509-779-3-copy-141-264.rst, result 5) and that Marra et al (AA230335) Genbank Sequence Database (Acession AA230335), National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland, publicly available February 26, 1997 teaches a DNA molecule that comprises 99.5% of residues 63-634 of SEQ ID NO:1 (which was found in us-09-509-779-1.rst, result 50).

Claim Rejections - 35 USC § 112

13. Claims 2-6, 8-17, 25-26, 32 and 38-40 and 42 are rejected under 35 U.S.C. 112, first paragraph.

Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

Some of Applicants arguments drawn to the rejections of claims 2-6, 8-17, 25-26, 32, 38-40 under 35 USC 112, first paragraph, are relevant to the instant rejection.

Applicant argues that with respect to diagnosis of cancer, the specification discloses, in Example 21, that cancer can be diagnosed using SAG as a marker and states that samples of both normal and tumor tissue from 12 patients were analyzed using routine technologies. The argument has been considered but has not been found persuasive for the reasons set forth previously and above. Further, a careful review of Example 21 reveals that the example is ambiguously written and never states that any analysis was done on the tissues or that any differential between normal and tumor tissue was found. The specification states only that a finding of a differential indicates that there is a tumor specific mutation.

Applicant argues that the present invention is useful for a laundry list of applications and cites specific *in vitro* assays taught in the specification that enable the claimed invention and states that there is no requirement under 35 USC 112 first paragraph to include human or clinical data or working examples if the description of the invention itself is sufficient to permit one skilled in the art to make and use the

invention as is the case here. The argument has been considered but has not been found persuasive for the reasons set forth previously and above.

Applicant further argues that the specification teaches SEQ ID NO:1 and 3 as well as DNA molecules substantially similar to SEQ ID Nos 1 and 3 and that the specification teaches that SAG deletion mutants not only associate with cancer but are cancer specific and points once again to Example 21. The argument has been considered but has not been found persuasive for the reasons set forth previously and above.

Applicant further argues that the specification reveals *in vitro* methods of inhibiting growth of mammalian or non-mammalian cells with antisense constructs and states that there is no requirement under 35 USC 112 first paragraph to include human or clinical data or working examples if the description of the invention itself is sufficient to permit one skilled in the art to make and use the invention as is the case here. The argument has been considered but has not been found persuasive for the reasons previously set forth and set forth above.

14. Claims 2, 4-5, 8, 10-11, 39, 40, 42 are rejected under 35 USC 112, first paragraph as the specification does not contain a written description of the claimed invention. The limitations of a polypeptide that comprises at least one heme binding site and/or one zinc finger have no clear support in the specification and the claims as originally filed. A review of the specification discloses support for a nucleotide sequence that hybridizes to SEQ ID NO:1 and/or SEQ ID NO:3 under high stringency hybridization conditions wherein these DNA sequence can be used to direct expression of the SAG protein and the mutational analysis of SAG protein

function (para bridging pages 5-6), support for SAG protein with two imperfect heme binding sites and one imperfect zinc ring finger domain (p. 15, lines 28-33), support for a mutant which does not encode the zinc ring-finger motif (p. 29, line 27) but reveals no nexus between the disclosed hybridization conditions and the specifically claimed hybridizing DNA molecules and no support for the newly amended and added claims as currently constituted. The subject matter claimed in claims 2, 4-5, 8, 10-11, 39, 40, 42 broadens the scope of the invention as originally disclosed in the specification.

15. If Applicant were able to overcome the rejections set forth previously and above, Claims 2-5, 6 (if not drawn to SEQ ID NO:3), 8, 10-11, 12-14 (if not drawn to SEQ ID NO:3), 15-17, 32, 38-40 and 42 would still be rejected under 35 USC 112, first paragraph, because the specification while enabling for a human SAG polynucleotide, SEQ ID NO:3 and its complete complement does not reasonably provide enablement for any of the various polynucleotides associated with SEQ ID NO:3 by hybridization conditions as claimed, SEQ ID NO:1 or any of the various polynucleotides associated with SEQ ID NO:1 by hybridization conditions or any of the synthetic deletion mutants claimed or any of the deletion mutants of human cell lines claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to various polynucleotides associated with SEQ ID NO:3 by hybridization conditions as claimed, SEQ ID NO:1 or any of the various polynucleotides associated with SEQ ID NO:1 by hybridization conditions or any of

the synthetic deletion mutants claimed or any of the deletion mutants of human cell lines claimed. This includes synthetic polynucleotides with no known expression or function *in vivo*, Hybridization polynucleotides comprising fragments of SEQ ID Nos 1 and 3 and deletion mutants from cell lines wherein there is no established nexus between the cell line mutants and any *in vivo* condition or disease.

In particular, the claims drawn to hybridizing DNA molecules read on DNA molecules that partially hybridize to SEQ ID NO:1 and SEQ ID NO:3. The claims as written do not require that the DNA molecule hybridize to the complete sequence of SEQ ID NO:1 or 3 but only require that the polypeptide or protein encoded by said DNA molecule comprise at least one heme binding site and/or one zinc finger domain. Clearly, species that hybridize to a partial sequence of SEQ ID NO:1 and SEQ ID NO:3 as well as partially hybridizing species are included in the claims as currently constituted. It is well known in the art as taught by Kennel (Progr. Nucl. Acid Res. Mol. Biol., 1971, 11:259-301) that "depending on the G+C content, the minimum size for a stable complex is from 10 to 20 nucleotides. The thermal stability rises sharply for longer lengths so that, depending on the G+C content, the stability of a complementary duplex of 25-50 nucleotides approaches that of any much longer complex (p. 261). Given that the putative heme binding motif consists of 5 codons (or 18 nucleic acids) and the zinc finger domain consists of apparently 8 codons (or 24 nucleic acids), the claims clearly read on fragments that do not possess either the structure or functions contemplated for SEQ ID Nos 1 and 3 in the specification. Further, given that a complementary duplex of 25-50 nucleotides would be expected to hybridize under the claimed conditions, even if other segments

of the molecule are left hanging, it would be expected that the claims as written would read on a whole universe of DNA molecules without the structure or function of SEQ ID NO:1 or 3. In particular as drawn to the polypeptides encoded by the claimed variant DNA molecules, Bowie et al, of record, teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al, of record, who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al, of record, who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of

the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Given the above the function of the proteins encoded by the claimed variant DNA molecules cannot be predicted based on homology of SEQ ID NO:2 with SEQ ID NO:4. Applicant has not taught how to use the broadly claimed molecules or the polypeptides that are encoded thereby.

Further, as drawn to the synthetic deletion mutants or the polypeptides encoded thereby, the specification does not teach how to use these mutants other than for mutational analysis of SEQ ID NO:3, which for the reasons set forth above, is not a use that meets the requirements of 35 USC 112, first paragraph or 35 USC 101.

As drawn to the cell culture deletion mutants, as set forth previously and above, it cannot be predicted how to use the mutants because it cannot be determined from the information in the specification whether these deletion mutations are artifacts of the cell culture system or whether they have any connection with cancer.

Further, as drawn to the disclosed uses for SEQ ID NO:1, i.e. in cancer diagnosis and gene therapy there is no information in the specification as to whether or not SEQ ID NO:1 is in any way associated with primary cancer or whether SEQ ID NO:1 has deletion mutants in any type of primary cancer.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art

to predict how to use the claimed invention with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

16. If Applicant were able to overcome the rejections set forth previously and above, Claims 25-26 would still be rejected under 35 USC 112, first paragraph, because the specification while enabling for a diagnostic method for identifying colon cancer cells by detecting 7bp and/or 48 bp deletion mutation of SEQ ID NO:3 with PCR assay using primers that flank the region amplified by SEQ ID NOs 7 and 8, does not does not reasonably provide enablement for a method for identifying cancer cells by detecting mutations in a gene encoding a redox-sensitive protein that protects cells from apoptosis comprising subjecting an extract of the cells to PCR amplification using primers have a sequence comprised by the DNA sequences of claims 2, 3, 8, 9, 15. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to diagnostic assay for identifying cancer cells by detecting cells containing mutations in a gene encoding a redox-sensitive protein that protect cells from apoptosis. This includes identification of any type of cancer cell, with any type of mutation in any gene encoding a redox-sensitive protein that protects from apoptosis with a PCR primer having any sequence comprised by a DNA sequence which hybridizes to SEQ ID NO. 1 or 3 under the claimed conditions (which includes fragments of SEQ ID NO:3 and 1 and DNA molecules that partially hybridize to SEQ ID NO:3 and SEQ ID NO:1) as well as primers from

synthetic mutants that are not found in nature which for the reasons above are not enabled and further which include a whole universe of primers that do not even amplify the region in which the deletions identified in the cell lines were found..

The specification teaches that two deletion mutants of SEQ ID NO:3 were isolated from DLD-1 colon carcinoma cells using primers SEQ ID NO:7 and 8, wherein SEQ ID NO:11 is a frame shift deletion, resulting from a 7 bp deletion, that abolishes the zinc-finger motif and SEQ ID NO:13 is an in-frame deletion, resulting from a 48 bp deletion, that eliminates 16 amino acids in the encoded protein but retains the zinc-ring finger motif (p. 26) and that 7 base pair and 48 base pair deletions were detected in the CATES-1B cell line, a testicular carcinoma cell line (p.27). Although 20 different types of cancer cell lines were assayed, only two were found to contain deletion mutants of SEQ ID NO:3. The specification concludes that these results indicate that the SAG deletion mutations occur very rarely in human cell lines (p. 26). The specification appears to exemplify human cancer diagnosis using SAG as a marker in a prophetic example in the specification, paragraph bridging pages 33-34. It is again noted that no data is presented, the specification never states that the assays were done or whether or how many of the colon carcinomas tested had deletion mutations of SEQ ID NO:3. The specification does not exemplify the assay of primary testicular carcinoma samples compared to normal control.

One cannot extrapolate the teaching of the specification to the scope of the claims because, for the reasons set forth previously and above, no one of ordinary skill in the art would believe that it was more likely than not, in the absence of

objective evidence demonstrating the nexus between the deletion in the cell line and primary carcinoma , that the deletion mutants found in the colon carcinoma cell line would be found also in primary colon carcinomas because of the well known artifactural nature of cell lines. It is noted that the apparent prophetic Example 21 does not enable the claimed invention as drawn to colon cancer. For the same reasons, that is the artifactural nature of cell lines, no one of ordinary skill in the art would believe that it was more likely than not, in the absence of objective evidence demonstrating the nexus between the deletion in the testicular carcinoma cell line and primary testicular carcinoma that the invention could diagnostically identify primary testicular carcinoma cells. Further, even if, as the specification infers, one were to believe that deletion mutation in cell lines can be directly correlated to deletions mutations in primary cancers, the specification makes clear that deletion mutation of SEQ ID NO:3 is a rare event in tumor cell lines. Given this teaching, no one of skill in the art would accept the hypothesis that the instantly claimed method could be used for the diagnostic identification of cancer cells as currently broadly claimed. In addition, given that the deletion mutations were identified only in the region flanked by SEQ ID NOS 7 and 8, even if it were to be found that the identification of deletion mutation is indeed diagnostic of colon cancer or testicular cancer, it could not be predicted, nor would it be expected that primers to regions that do not include the region flanked by SEQ ID NOS 7 and 8 would detect said deletion mutations. Finally, as drawn to diagnostic assay by detecting "mutations", the specification teaches that two tumor cell lines were found to have one or both of two specific deletions, a 7bp deletion and a 48 bp deletion and no other mutations

have been identified. Given in the information in the specification, it cannot be predicted that other mutations would be found in the SEQ ID NO:3 gene and it cannot be predicted whether, if found, they would be in any way associated with cancer.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict how to use the claimed invention with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

17. Claims 25 and 26 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 25-26 are drawn to a diagnostic assay for identifying cancer cells by detecting cells containing mutations in a gene encoding a redox-sensitive protein that protects cells from apoptosis, comprising subjecting said nucleic acid molecules to amplification with primers and determining whether the resulting PCR product contains a mutation. Although drawn to DNA product arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of

a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The

Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of a gene encoding a redox-sensitive protein that protects cells from apoptosis and that is useful for identifying cancer cells and "mutations" that are diagnostic for identifying cancer cells, per Lilly by structurally describing a representative number of genes encoding a redox-sensitive protein that protects cells from apoptosis and that are useful for identifying cancer cells and "mutations" that are diagnostic for identifying cancer cells or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the genes encoding a redox-sensitive protein that protects cells from apoptosis and that are useful for identifying cancer cells and "mutations" that are diagnostic for identifying cancer cells required to practice the method of claims 25-26 in a manner that satisfies either the Lilly or Enzo standards. Even if it were to be established that SEQ ID NO:3 is a gene encoding a redox-sensitive protein that protects cells from apoptosis and that is useful for identifying cancer and that the 7bp and 48 bp mutations could be used to diagnose colon cancer or testicular cancer, this single example of SEQ ID NO:3 and the 7bp and 48 bp deletion mutations of SEQ ID NO:3 do not provide a description of genes encoding a redox-sensitive protein that protects cells from apoptosis and that are useful for identifying cancer cells and "mutations" that are diagnostic for identifying cancer cells that would satisfy the standard set out in Enzo because the specification does not disclose sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics that would identify the claimed genus.

The specification also fails to describe the genes encoding a redox-sensitive protein that protects cells from apoptosis and that are useful for identifying cancer cells and "mutations" that are diagnostic for identifying cancer cells required to practice the method of claims by the test set out in Lilly. In this case, even if it were to be established that SEQ ID NO:3 is a gene encoding a redox-sensitive protein that protects cells from apoptosis and that is useful for identifying cancer and that the 7 bp and 48 bp mutations could be used to diagnose colon cancer or testicular

cancer, the specification describes only a single gene encoding a redox-sensitive protein that protects cells from apoptosis and that are useful for identifying cancer cells and a single set of deletion mutations of that gene that are diagnostic for identifying cancer cells required to practice the method of claims . Therefore, the specification necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, even if it were to established that SEQ ID NO:3 is a gene encoding a redox-sensitive protein that protects cells from apoptosis and that is useful foridentifying cancer and that the 7bp and 48 bp mutations could be used to diagnose colon cancer or testicular cancer the specification does not provide an adequate written description of the genes encoding a redox-sensitive protein that protects cells from apoptosis and that are useful for identifying cancer cells and "mutations" that are diagnostic for identifying cancer cells that is required to practice the claimed invention. Since the specification fails to adequately describe the product to must be used to practice the invention, or the mutations that would be useful for diagnostically identifying cancer cells, it also fails to adequately describe claimed diagnostic assay and the claims are not adequately supported by an adequate written description.

18. No claims allowed.

19. All other objections and rejections recited in Paper No. 17 are withdrawn.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Susan Ungar
Primary Patent Examiner
November 6, 2003